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EXAMINER	
SANG, HONG	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,037	DEBATIN ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-44* is/are pending in the application.

4a) Of the above claim(s) *35-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-34 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Debatin et al.

1. Applicant's election with traverse of Group I (claims 23-34 and 44) and species election of TAT, doxorubicin and neuroblastoma in the reply filed on 7/25/07 is acknowledged. The traversal is on the ground(s) that the search and examination of the four different groups of claims is not unduly burdensome. This is not found persuasive because the instant case is a national stage filing of an international application (i.e. 35 U.S.C. 371) and therefore the standard of burdensome search is not applied. As indicated in the last office action the technical feature linking the inventions is not novel and does not provide contribution over the prior art (see previous office action, page 3), as such, unity of invention is lacking and the inventions are deemed to be separate. Because of these reasons, the requirement is still deemed proper and is therefore made FINAL.

2. The information disclosure statement (IDS) filed on 10/13/2004 has been considered. A signed copy is attached hereto.

3. Claims 23-44 are pending. New claim 44 is added. Claims 1-22 are cancelled. Claims 35-43 are withdrawn from further consideration as being drawn to non-elected inventions.

4. Claims 23-34 and 44 are under examination. Due to species election, claims are examined to the extent that the carrier is TAT and cytostatic compound is doxorubincin.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

6. Claims 24-29 are objected to because of the following informalities: the recitation of the phrase "wherein said protein" in claim 24 appears to be a mistake because said protein would mean Smac, not TAT. It should be changed to "wherein said carrier".

7. Claim 26 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 25 limits the fragments or derivative of the TAT protein to "comprising the amino acids 37 to 72 of TAT". Claim 26, which depends from claim 25, limits the fragments or derivative of the TAT protein to "comprising the amino acids 37 to 57 of TAT". Therefore, claim 26 fails to further limit the fragments or derivative of the TAT protein of claim 25. Claim 26 would be in proper dependent form if it was dependent from claim 24.

8. Claims 28 and 29 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 27 limits the fragments or derivative of Smac to a peptide to a peptide comprising the amino acid sequence 56 to 70 of Smac. Claims 28 and 29, which depend from claim 27, limit the fragments or derivative of Smac to a peptide comprising the amino acid sequence 56-62, and 56 to 69 of Smac, respectively. Therefore, claims 28 and 29 fail to further limit the fragments or derivative of Smac of claim 27. Claim 28 and 29 would be in proper dependent form if they were dependent from claim 26.

9. Claim 27 is objected to because of the following informalities: claim 27 recite "comprising the amino acid sequence 56 to 70". For clarity, claim should be amended to recite "comprising the amino acid sequence 56 to 70 of Smac".

10. Claim 30 is objected to because of the following informalities: claim 30 recites "wherein the Smac protein is a fragment or derivative comprising amino acids 56 to 62 or 56 to 59 of Smac. However, the claim has already defined Smac protein as the protein disclosed by GenBank accession number AAF87716 on line 2 of the claim (accession number is full length of the Smac protein). Therefore, the claim should be amended to recite "wherein the fragment or derivative comprises amino acids 56 to 62 or 56 to 59 of Smac".

11. Claim 33 is objected to because a Markush-type claim should recite alternatives in a format such as "selected from the group consisting of A, B and C." see MPEP § 803.02.

Claim 33 should be amended to add the term "and" before the term "amilomer" (the last compound listed).

12. Claims 25-30 are objected to because the term "aminoacid" should be spelled "amino acid".

Claim Rejections - 35 USC § 112, 2nd paragraph

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 23-34 and 44 are rejected as vague and indefinite for reciting GenBank Accession Number. It is well known in the art that accession numbers can be altered, deleted, amended, or revised over time by various inventors. Hence, one of ordinary skill in the art would be unable to discern the bounds of the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 23-34 and 44 are rejected under 35 U.S.C. 1 12, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims recite the GenBank accession numbers AAF87716 and CAA49921, which appear to be essential material to the practice of the instant invention. Such incorporation is not seen as sufficient so as to enable the skilled artisan to make and use the instant invention.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an

allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

If applicant intends to comply with incorporation by reference by providing a sequence listing, applicant is reminded to provide said Sequence Listing which complies with the requirements of 37 CFR 1.821 through 1.825 for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded to provide the appropriate Hawkins Declaration to accompany amending the instant specification to provide the essential subject of the "amino acid sequence" defining the claimed "Smac protein" and "TAT protein".

Claim Rejections - 35 USC § 112, 1st paragraph

17. Claims 23-26, 31-34 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is Written Description rejection.

Claims recite "Smac protein, fragments or derivatives thereof" and "TAT protein, or a fragment or derivative thereof" (see claim 23 for example"). The specification on page 4 teaches that in the context of the present invention, the term derivative or fragment of the Smac protein refers to peptides in which one or more amino acids of the sequence of 239 amino acids, as disclosed in GenBank number AAF87716, can be substituted by one or more amino acids different from the original one(s), or peptides the amino acid sequence of which is either extended, shortened, or both, on either the amino terminal, or the carboxyl terminal or both ends with respect to the original Smac proteins, provided that the function of the Smac protein remains unaffected. The specification on page 5 teaches that when a protein is used as a carrier, the term derivative or fragment of a protein refers to peptides in which one or more amino acids can be substituted by other amino acids different from the original one(s), or peptides the amino acid sequence of which is either extended, shortened, or both, on either the

amino terminal, or the carboxyl terminal or both ends, with respect to the original one(s), provided that the function as a carrier for the cellular uptake of Smac remains unaffected. The instant specification only teaches fragments of Smac that are 56-70, 56-62 and 56-59 of Smac (see page 4, lines 21-26, and page 18, lines 25-30) and 37-72 and 47-57 of TAT protein (see page 6, lines 6-14). The specification does not disclose any derivatives of Smac and TAT protein. Therefore the written description is not commensurate in scope with the claims which read on any and all fragments and derivatives of Smac and TAT protein. There is a lack of written description regarding the structural characteristics of the claimed fragments and derivatives of Smac protein and TAT protein. There is a lack of a written description regarding which amino acids within the full-length of Smac and TAT protein can be changed by deletion, addition, substitution and/or combination thereof, such that the resulting fragments, homologs, and derivatives still have the same function as the full length protein.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the

genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Although drawn to DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University Of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The Court stated that" [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. at 1567, 43 USPQ2d at 1405. The court also stated that:

> *a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.*

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be

described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See *Enzo Biochem, Inc. V. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics .... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in *Lilly* and *Enzo* were DNA constructs *per se*, the holdings of those cases are also applicable to claims such as those at issue here. Thus the instant specification may provide an adequate written description of fragments and derivatives of Smac protein and TAT protein, per *Lilly*, by structurally describing representative fragments and derivatives by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics,

functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe an amino acid that is a fragment or derivative of Smac or TAT protein that is useful in the claimed invention in a manner that satisfies either the *Lilly* or *Enzo* standards. Although the specification discloses 56-70, 56-62 or 56-59 as fragments of Smac, and 37-72, 47-57 as fragments for TAT, this does not provide a description of the broadly claimed fragments and derivatives that would satisfy the standard set out in *Enzo* because the specification provides no functional characteristics coupled to structural features, which characteristic and features are shared by a substantial number of the members of the genus.

Further, the specification also fails to describe an amino acid that is a fragment or derivative of Smac protein or TAT protein by the test set out in *Lilly* because the specification describes only 56-70, 56-62 or 56-59 as fragments of Smac, and 37-72, 47-57 as fragments for TAT. Therefore it necessarily fails to describe a representative number of such species for the broadly claimed fragments and derivatives. Thus the specification does not provide an adequate written description of an amino acid that is a fragment and derivative of Smac and TAT protein that is required to practice the claimed invention.

That is, the specification provides neither a representative number of the fragments and derivatives of Smac and TAT, nor does it provide a descriptive of structural features that are common to the fragments and derivatives. Since the disclosure fails to describe the common attributes or characteristics that identify

members of the genus, and because the genus is highly variant, the disclosure of a 56-70, 56-62 or 56-59 as fragments of Smac, and 37-72, 47-57 as fragments for TAT is insufficient to describe a highly variant genus (any fragments and derivatives of Smac or TAT protein). Because the genus of molecules encompassed by the term "fragments and derivatives" is extensive and the artisan cannot envision the detailed structure of the encompassed fragment and derivatives therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus one of skill in the art would not be able to recognize that applicant was in possession of the invention as now claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Therefore, only the full length of Smac protein, 56-70, 56-62 and 56-59 fragments of Smac protein, full length of TAT protein, and 37-72, 47-57 fragments of TAT protein but not the full breadth of "fragments and derivatives" meet the written description provision of 35 U.S.C. § 112 first paragraph. Applicant is reminded that *Vas-Cath*

makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claim Rejections - 35 USC § 112, 1st paragraph

18. Claims 23-26, 31-34 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Smac protein/carrier entity, a drug, a medicament for treatment of cancer comprising the Smac protein/carrier entity, wherein said Smac protein/carrier entity comprising a full length Smac protein, or a Smac peptide consisting of the amino acid fragment 56-70, 56-62, or 56-59 of the full length Smac protein, and a carrier that is full length TAT protein, or the protein transduction domain of TAT consisting of the amino acid fragment 37-72, or 47-57 of the full length TAT protein, does not reasonably provide enablement for a Smac protein/carrier entity, a drug, a medicament for treatment of cancer comprising the Smac protein/carrier entity, wherein said Smac/carrier entity comprising any and all fragments or derivative of the full length Smac protein, and a carrier that is any and all fragments or derivatives of the full length TAT protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims 23-26, 31-34 and 44 are drawn to a Smac protein/carrier entity, a drug, and medicament for treating a cancer comprising the Smac/protein/carrier entity, wherein the Smac protein/carrier entity comprising a full length of a Smac protein, or a derivative or fragment thereof, and a carrier wherein the carrier is the full length of a TAT protein, or a fragment, derivative thereof.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The specification on page 4 teaches that in the context of the present invention, the term derivative or fragment of the Smac protein refers to peptides in which one or more amino acids of the sequence of 239 amino acids, as disclosed in GenBank number AAF87716, can be substituted by one or more amino acids different from the original one(s), or peptides the amino acid sequence of which is either extended, shortened, or both, on either the amino terminal, or the carboxyl terminal or both ends with respect to the original Smac proteins, provided that the function of the Smac protein remains unaffected. The specification on page 5 teaches that when a protein is used as a carrier, the term derivative or fragment of a protein refers to peptides in which

one or more amino acids can be substituted by other amino acids different from the original one(s), or peptides the amino acid sequence of which is either extended, shortened, or both, on either the amino terminal, or the carboxyl terminal or both ends, with respect to the original one(s), provided that the function as a carrier for the cellular uptake of Smac remains unaffected.

In view of the teachings of the specification, the breadth of the claims is very broad.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the structure and function of the fragments, and derivatives of the full length of Smac and TAT proteins. Moreover, it would require undue experimentation to determine which of the protein fragments, or derivatives of Smac protein and TAT protein are in fact capable of treating cancer. The identification and characterization of each of these protein fragments, and derivatives would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

Moreover, the quantity of experimentation in the areas of cancer treatment is extremely large given the unpredictability associated with cancer treatment, the lack of correlation of *in vitro* findings to *in vivo* success, animal study to human treatment.

One cannot extrapolate the teachings of the specification to the scope of the claims because the specification only teaches a method of sensitizing resistant tumor

cells for death receptor or drug-induced apoptosis using a Smac protein/carrier entity wherein the Smac protein is a full length protein or fragments of 56-62 thereof, the carrier is TAT protein, or the protein transduction domain thereof, and the claims are broadly drawn to method of treating any and all cancer using a Smac protein/carrier protein comprising any and all fragments, and derivatives of Smac and TAT protein, and applicant has not enabled all of these types of Smac protein/carrier entity because it has not been shown that these Smac protein/TAT entity that comprises any and all fragments thereof are capable of inducing apoptosis of cancer cells.

The state of the prior art and the predictability or lack thereof in the art:

Protein chemistry is probably one of the most unpredictable areas of biotechnology. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha,

replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make all the fragments, and derivatives of Smac and TAT proteins that are capable of treating cancer. Therefore, it is not clear what criteria would be used in deciding which amino acids and how many of them would and could be substituted in the wild type protein.

Treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of

potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Experimental evaluation of new anticancer agents is realized by means of in vitro and in vivo methods to describe whether or not a new drug is effective against cancer cells. Even if a candidate drug inhibits cancer cell proliferation in vitro, it is still unpredictable where this drug will be effective in treating cancer in vivo, such as in an animal model.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of

Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Zips et al. (In Vivo, 2005, 19:1-8) teach that "It is obvious that cells in culture represent an artificial and simplified system.

Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential."

All of this underscores the criticality of providing workable examples in the specification, particularly in an unpredictable art such as cancer treatment.

Working examples

The specification teaches that overexpression of Smac in SHEP neuroblastoma cells by transfecting the cells with a full length Smac construct potentiated TRAIL-induced apoptosis in a dose- and time-dependent manner compared to vector control cells, and also markedly increased apoptosis induced by anti-CD95 antibody, or cytotoxic drugs (see page 17). The specification teaches that Smac sensitizes for apoptosis by antagonizing XIAP (see page 17). The specification teaches that cytosolic Smac bypass the Bcl-2 inhibition (see page 17). The specification teaches that Smac peptide (i.e. the N-terminal 4 residues of Smac together with the 3 following residues, which the examiner believes to be the 56-62 amino acid residue of Smac protein according to page 4,lines 26 of the specification), which is linked to the protein transduction domain of the TAT protein (the residue 47-57 of TAT protein according to page 6, line 12) sensitizes resistant tumor cells in vitro for death receptor or drug-

induced apoptosis (see page 17). The specification teaches that Smac peptides enhance the anti-tumor effect of TRAIL in glioblastoma in vivo and induce eradication of tumors (see specification page 19). However, except the full length Smac protein and the Smac peptide consisting of 56-62 fragment thereof, linked to the protein transduction domain of the TAT protein consisting of 47-57 of TAT protein, the specification does not teach any other Smac fragments or derivatives linked to any other fragments or derivative of TAT protein, which are capable of inducing apoptosis or treating cancer.

Guidance in the specification

While one of ordinary skill in the art can theoretically produce all of these modified proteins with art known techniques such as site-directed mutagenesis it would still be burdensome to one of ordinary skill in the art to produce all of these different combinations and thereafter determine their activity. It is art known that certain residues are shown to particularly important to the biological or structural properties of a protein or peptide, e.g., residues in active sites and such residues may not be generally be exchanged. Skolnick et al teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (Skolnick, et al. Trends in Biotech. 18, 34-39, 2000, see abstract, in particular). Given the unlimited number of undisclosed fragments and derivatives, there is no evidence indicating that the broadly claimed fragments and derivative can still induce apoptosis or treat cancer. Furthermore, it is not clear what criteria would be used in deciding which amino acids

and how many of them would and could be substituted in the wild type protein. Without such guidance, the changes which can be made in the protein structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016 and Ex parte Forman, 230 USPQ 546 (BPAI 1986). For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Level of skill in the art

The level of the skill in the art is deemed to be high

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue that all fragments and derivatives can induce apoptosis and treat cancer and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 23-34 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alnemri (WO 02/16418A2, Pub. Date: 2/28/2002, IDS), in view of Wang (WO 02/16402, Pub. Date: 2/28/2002, IDS), and Ford et al. (Gene Therapy, 2001, 8: 1-4).

Alnemri teaches a composition for inducing cancer cell apoptosis comprising an isolated Smac peptide or polypeptide comprising the residue 56-139 of SEQ ID NO.1, and a physiologically acceptable carrier (see page 6, lines 3-6, the paragraph bridging pages 6-7, page 18, lines 1-2, page 37, claims 52, 53 and 88). Alnemri teaches mature Smac that is a Smac polypeptide without the 55 amino acid residue mitochondrial targeting sequence (MTS) (see page 12, lines 9-11), the first 7 residues of mature Smac, Smac-N7, SEQ ID NO.6 and the first 35 residues of mature Smac, Smac-N35, SEQ ID NO.11 (see the paragraph bridging pages 46-47). Alnemri teaches that short peptides derived from the N-terminus of mature Smac (e.g. Smac-N7, and Smac-N35) could be used as promoters of caspase enzymatic activity at attainable concentrations to kill cancer cells that overexpress IAPs (see the paragraph bridging pages 46-47). Alnemri teaches that the Smac peptides or polypeptides are human Smac (see page 41, Example 1).

Alnemri does not teach that a Smac peptide or polypeptide that is linked to the amino acid domain 37-72 or 47-57 of the TAT protein via a chemical bond. Alnemri does not teach that the composition of the Smac polypeptide further comprises a cytostatic compound such as doxorubicin. However, these deficiencies are made up for in the teachings of Wang and Ford et al.

Wang et al. teach a pharmaceutical composition for inducing cancer cell apoptosis comprising a therapeutically effective amount of the AV peptide, and further comprising an additional therapeutic agent such as an anti-neoproliferative chemotherapeutic agent, and a pharmaceutical acceptable carrier (see page 3, lines 1st -3rd paragraph, page 14, 2nd paragraph, page 18, claims 1-8), wherein the AV peptoid is the residue 56-59, 56-60, 56-61, 56-62 of the full length Smac protein (see page 28, Table).

Ford et al. teach that large molecules (β-galactosidase, horseradish peroxidase etc), when chemically cross-linked with TAT peptides (either amino acids 1-72 or 37-72) were taken up by cells in vitro and in vivo (see page 2, 2nd column). Ford et al. disclose that the still smaller TAT protein basic domain (37-47 amino acids) rapidly translocated through the plasma membrane and accumulated in the nucleus (see page 2, 2nd column). Ford et al. disclose efficient cellular uptake of a small peptide conjugated to the TAT peptide (see page 2, 2nd column). Ford et al. teach that TAT-mediated delivery can be improved by constructing fusion proteins between several polypeptides and proteins and the 47-57 region of the TAT protein (see page 2, 2nd column). Ford et al. disclose that many proteins have been successfully transported into a wide variety of

human and murine cell type, using the TAT PTD methodology (see page 2, 2nd column, 3rd paragraph). Ford et al. disclose that the fact that PTDs can cross the blood brain barrier may also make them suitable for a range of neurological applications (see page 3). Ford et al. disclose that PTD may provide efficient means of intracellular delivery of not just proteins, but macromolecules such as DNA as well as cancer chemotherapeutic agents (e.g. doxorubicin).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to chemically link the Smac peptide or polypeptide of Alnemri or Wang to the 37-72 or 47-57 residue of TAT protein in view of the teachings of Ford. One would have been motivated to do so because Ford et al. teach that proteins when linked to the 37-72 or 47-57 residue of TAT protein can be effectively delivered into cell cytoplasm or nucleus. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to chemically link the Smac peptide or polypeptide of Alnemri or Wang to the 37-72 or 47-57 residue of TAT protein because Ford et al. teach that many proteins have been successfully transported into a wide variety of human and murine cell type, using the TAT PTD methodology.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, one would have been motivated to include doxorubicin in the composition of Alnemri or Wang because Wang et al. teach a composition comprising a Smac peptide and a chemotherapeutic agent, and doxorubicin is a well known chemotherapeutic agent as shown by Ford.

While the prior art does not specifically mention the gene accession number recited in the claims, because the prior art teaches the human mature Smac and N-terminal domain thereof, and the PTD domain of the TAT protein, the amino acid sequences disclosed by the gene accession numbers are considered inherent property of the Smac and TAT proteins.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
September 10, 2007

/Christopher Yaen/
Primary Examiner
Art Unit 1643
September 13, 2007